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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,911	06/07/2006	Naoko Kida	Q95279	8940

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EXAMINER	
UNDERDAHL, THANE E	

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,911	KIDA ET AL.	
	Examiner	Art Unit	
	THANE UNDERDAHL	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3, 5-7 and 9-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-7 and 9-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This Office Action is in response to the Applicant's reply received 7/28/08. Claims 1-3, 5-7 and 9-11 are pending. No claims are withdrawn. Claims 4 and 8 are cancelled. Claim 1 has been amended. No claims are new.

Response to Applicant's Arguments— 35 U.S.C § 103

In the response submitted by the Applicant, the 35 U.S.C § 103 (a) rejection of claims 1-3, 5, 6, 9-11 over Goodwin #1, Goodwin #2, Goodwin #3, and Schwarz et al. in light of support from Unsworth et al., Wikipedia, Bock et al. and Bartlett were considered but not found persuasive.

The Applicant argues that the Examiner has not recognized that the order of the steps of the method. The Examiner is aware that the culturing of the 2D cultures to confluence occurs before the 3D culture and states such in the review of the claims on pg 3 of the previous office action (see bulleted items at the bottom of the page). The Examiner also stated that Goodwin #1 first seeded the cells on a matrix then placed them in a RVW for 3D culture (previous Office Action, Pg 4, 2nd paragraph). The arguments that the 3D culture was subcultured to the confluent 2D culture (Applicant's Response, pg 5, lines 1-7) are noted, however the Examiner made no such statement indicating the process steps occurred in reverse.

The Applicant argues that:

> "one of ordinary skill in the art would have no reasonable expectation of success in incorporating the confluent 2D culture of chondrocytes or ovarian tumor cells in the culture of mesenchymal cells because it is well-known in the art that the properties of undifferentiated mesenchymal cells are different from those of fully differentiated chondrocytes or ovarian tumor cells" (Applicant's Response, pg 5, last paragraph).

The Applicant further argues that:

> "Moreover, the confluent 2D culture prior to subculturing is out of the common general knowledge in the field of cell culture. A person skilled in the art normally subcultures the cells when the cells grow to 70 to 90% confluency. It is known in the art that, if the cells are cultured to 100% confluency, then the proliferation property of the cells may be affected or the phenotype of the cells may alter due to contact inhibition. Thus, it is atypical to conduct the confluent 2D culture prior to subculturing." (Applicant's Response, pg 6, last Full paragraph).

However culturing many 2D cells to confluency is an common technique in the art and ubiquitous in cell culture as supported by Current Protocols in Cell Biology (Unit 1.1.1 and 1.1.9 Critical Parameters). Indeed Current Protocols teaches that "Cultures should be 75% to 100% confluent when selected for subculture. Growth in culture will be adversely affected if cells are allowed to become overgrown." (Unit 1.1.9, col 2, Critical Parameters). Provided that Current Protocols refers to cells in the generic terms and does not provide any exceptions therefore it would be obvious to one of ordinary skill in the art to culture cells to confluence when using traditional 2D culture techniques and have a reasonable expectation of success. Also the teachings of previously cited art of Bock et al. (pg 107) and Bartlett et al. (pg 163, step 2) support the concept that culturing cells to confluence is a generic technique in the art, applicable to many cell types, since they culture two distinct cell lines, with distinct properties, to confluence with success. Therefore in light of the above rational, the Office maintains its position that culturing cells 2D to confluence is a known technique in the art and that applying this known technique to the method of Goodwin #1 is obvious in the absence of evidence to the contrary or unexpected results.

The Applicant argues that Goodwin #1 teaches away from culturing cells to confluence, because as Goodwin #1 teach "Human bone marrow cell production declines

over time in monolayer culture" (Goodwin #1, col 4, lines 23-34). However this argument is not commensurate with the scope of the claims since this citation does not discuss the if the cells are grown to confluence or to what degree of confluence is optimum or detrimental to these cells. As mentioned in the previous office action, the two other references by Goodwin (Goodwin #2 and Goodwin #3) obviously culture their cells to confluence then subculture them in a RVW reactor, so it would be obvious to one ordinary skill in the art to apply those same method steps for this situation with bone marrow mesenchymal cells, since these method steps were already twice successful.

Applicants argue that their invention is not the expansion of bone marrow mesenchymal cells but the differentiation of these cells to cartilage tissue expressing Type II collagen. The Examiner address that Goodwin#1 does indeed meet these limitations in the previous action by producing cartilage tissue expressing Type II collagen from the bone marrow mesenchymal cells (Goodwin #1, col 13, lines 10-20).

Therefore the rejection stands and is repeated below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 6, 9-11 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Goodwin #1 (U.S. Patent # 5,496,722), Goodwin #2 (In Vitro. Cell Dev. Biol, vol 33, page 358, 1997), Goodwin #3 (In Vitro. Cell Dev. Biol, vol 33, page 366, 1997) and Schwarz et al. (U.S. Patent # 5026650) in light of support from Unsworth et al. (Nature Medicine, 1998) Wikipedia (Definition—Bone Marrow), Bock et al. (Tissue Engineering of Cartlage and Bone) and Bartlett (Ovarian Cancer Methods and Protocols).

These claims are to a method of making cartilage tissue comprising the following steps:

- 2-D culturing of bone marrow mesenchymal cells to confluence
- Subculturing the cells 3-D in a microgravity environment using a uniaxial rotary bioreactor that provides a simulated microgravity environment on earth via controlling the rotational speed of the bioreactor.
- Obtaining tissue expressing Type II collagen.

The claims further limit that the rotary bioreactor provides a gravity that is 1/10 to 1/100 of the ground gravity for an object for a time average basis and is the result of controlled rotation speed. The rotary bioreactor is a **Rotating Wall Vessel (RWV)** bioreactor. The cells are seeded in the bioreactor at a density of 10^6 to 10^7 cells/cm^3 at a rotational speed of 8.5 to 25 rpm in a 5 cm diameter RWV. This rotational speed is adjusted to minimize the influence of the ground gravity of the cells. The claims further limit that the bone marrow mesenchymal cells are isolated from a subject in need of a cartilage tissue transplant. The resulting cartilage tissue has a major axis of 1 cm or more.

Goodwin #1 teaches that a mixture of chondrocytes and stromal cells are obtained from bone marrow of mammalian femurs (Goodwin #1, col 12 lines 50-60 and col 13 lines 40-50). One of ordinary skill in the art would recognize that bone marrow mesenchymal cells are also called bone marrow stromal cells (as supported by Wikipedia-Bone Marrow). Therefore one of ordinary skill in the art would recognize that the cells obtained by Goodwin #1 comprise bone marrow mesenchymal cells. These cells are transferred to a fluid culture medium and suspended in culture medium at a density of $1X10^6$ cells/ml and seeded on a culture matrix. This seeded culture matrix was then placed in a RWV, preferably one taught by the incorporated reference of Schwarz et al. (Goodwin col 8, lines 5-10) that can simulate an environment of 10^{-2} of ground gravity as supported by Unsworth et al.(Unsworth et al., page 902, col 1). Goodwin #1 teach that culturing the mixture of bone marrow mesenchymal cells and chondrocytes produced cartilaginous tissue structures that contained Type II collagen (Goodwin #1, col 13, lines 14-19). Goodwin #1 teach that the cells were cultured up to 65 days and after 1000 hours (~42 days) produced a tissue mass at least 0.4 cm in length (Goodwin #1, col 13, lines10-20).

The RWV of Schwarz et al. can have a controlled rotation between 5 and 40 RPM (Schwarz, col 7, lines 5-10). Schwarz et al. teach that the rotation speed is increased and decreased to synchronize the falling cells with the rotating reactor so the cells are maintained floating in suspension (i.e. defy gravity) (Schwarz, Claim 3). Goodwin #1 also teach that the rotational speed of the RWV is adjusted to keep the cells in suspension and prevent collision of cells (Goodwin, col 8, lines 4-28).

What Goodwin #1 does not explicitly teach is that the bone marrow mesenchymal cells a first cultured to confluence then, subcultured in the RWV. One of ordinary skill in the art would recognize that expanding cells using traditional 2D culture flasks and then using those cells as an inoculum is a common practice in the art. This is supported by the teachings of Goodwin in two additional references (Goodwin #2 and Goodwin #3). These two references by the same author teach that the other cells such as chondrocytes and ovarian tumor cells are initially cultured with traditional 2D techniques before being subculture in the RWV. Goodwin #2 teach that chondrocytes are isolated from the specimen and expanded in 2D cell cultures for two passages to produce sufficient numbers of cells to inoculation and subculture in a RWV (Goodwin #2, pg 359, col 1, Cell isolation). One of ordinary skill in the art would recognize that chondrocytes (cartilage cells) are cultured to confluence before passage as supported by Bock et al. (pg 107, 2nd paragraph). So it would have been obvious to someone skilled in the art to culture cartilage cells to confluence and then passing the cells to expand the culture to provide a sufficient number of cells before subculturing them in the RWV.

Furthermore Goodwin #3 teach that ovarian tumor cells are cultured in traditional 2D flasks for multiple passages before being trypsinized and inoculated into the RWV (Goodwin #3 page 367, Col 1 RWV cultures). One of ordinary skill in the art would recognize that ovarian cancer cells like chondrocytes are grown to confluence before passage as supported by Bartlett (page 163).

It would have been obvious to someone skilled in the art to use traditional 2D culture methods to expand the cells bone marrow mesenchymal cells and chondrocytes

isolated from mammals by Goodwin #1 to grow the cells to confluence then inoculate them into the RWV for subculturing. Goodwin #2 and Goodwin #3 teach that this is common technique for isolated chondrocytes and for other cells such as ovarian tumor cells. This is a simple matter of applying known cell culture technique to expand and produce enough cells for an adequate sized inoculum for an RWV. This would be an obvious improvement over simply isolating the necessary cells every time an inoculum for the RWV was necessary and would cut down on the time per experiment and mammals sacrificed. Therefore since using the known techniques of 2D cell culture would improve the overall RWV method of Goodwin #1 and were used for two other cell types by Goodwin #2 and #3 with success it would have been obvious to someone skilled in the art to uses these known techniques to improve similar RWV methods (KSR International Co. v. Teleflex Inc., 550 U.S.--, 82 USPQ2d 1385 (2007)).

Neither of the references above teach the diameter of the RWV vessel or the concentrations of the cell concentrations needed to inoculate the RWV as limited in claim 6. However, one of ordinary skill in the art would recognize that limitations of vessel size and innoculum concentration are result effective variables. Absent any teaching of criticality by the applicant concerning these limitations, it would be *prima facie* obvious that one of ordinary skill in the art would recognize these limitations are result effective variables which can be met as a matter of routine optimization (M.P.E.P. § 2144.05 II).

Also while neither of the references above teach that cartilage tissue is formed of 1 cm or more this would have been obvious in view of the work of Goodwin #1. They teach that their bone marrow mesenchymal cells produce tissue masses of at least 0.4 cm in

length after 1000 hours of culture and that these cells were cultured for up to 65 days. Since one of ordinary skill in the art would recognize that the size of the tissue is directly related to the length of time in the RWV culture, it would have been obvious to someone skilled in the art that 1 cm long cartilage tissue could be formed given sufficient time. This is further supported by additional experimentation of Goodwin #1. They teach that other mesenchymal cells as well as epithelial cells were cultured for 45 days and did not reach a plateau phase and increased linearly as the culture progressed (Goodwin #1 col 9, lines 30-45).

Also claim 9 limits that the bone marrow mesenchymal cells are isolated from a subject in need of transplantation. The art is replete with references where bone marrow and cells are isolated from a subject. This is advantageous since these cells or their derivatives would be recognized as self by the subject and avoid inconvenient immunological side effects or even rejection of the cells if re-transplanted into the subject.

Therefore the references listed above renders obvious claims 1-3, 5, 6, 9-11.

Concerning the remaining 35 U.S.C § 103 (a) rejections in the Office Action the Applicant argues that since the amendments to claim 1 overcome the teachings of Goodwin #1, #2, #3 and Schwarz et al. in light of various supporting references over claims 1-3, 5, 6, 9-11 that they in turn overcome the remaining rejections that use these references. However as detailed above the Examiner disagrees and believes that the combination of Goodwin #1, #2, #3 and Schwarz et al. in light of supporting references is

proper and in the absence of arguments to the contrary these rejections stand for the amended claims and are repeated below.

Claims 1-3, 5-7, and 9-11 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Goodwin #1, #2, #3 and Schwarz et al. in light of various supporting references as applied to claims 1-3, 5, 6, 9-11 above, and further in view of Yan et al. (U. S. Patent Application Publication # 2002/0168763) and Simpson et al. (U. S. Patent Application Publication # 2002/0090725). The description and rejection of claims 1-3, 5, 6, 9-11 are described in the 35 U.S.C § 102(a) rejection above. Claim 7 further limits the method of claim 1 by requiring TGF- β and/or dexamethasone in the culture medium.

While Goodwin #1 teach that "various growth factors" may be added to the culture medium to "emulate *in situ* conditions" (Goodwin #1, col 4, lines 3-5). While Goodwin #1 does not specifically teach TGF- β this would be obvious to one of ordinary skill in the art at the time the invention was made in view of Simpson et al. who teach the addition of TGF- β to the culture medium (Simpson et al., paragraph 98) to grow collagen matrices in a microgravity reactor (Simpson et al., paragraph 207) that contain cells from bone marrow (Simpson et al., paragraph 204). It would have been obvious to someone skilled in the art to modify the invention of Goodwin #1 with the teachings of Simpson et al. since both culture bone marrow cells in a microgravity reactor. The motivation comes from Goodwin #1 who desires to create a culture that emulates *in situ* conditions and one of ordinary skill in the art would recognize that TGF- β would be present in the body where

bone marrow cells are cultured. The reasonable expectation of success is provided by Simpson et al. who teach the addition of TGF- β to the culture.

Likewise Goodwin #1 does not teach the addition of dexamethasone to their culture media, however this would be obvious at the time the invention was made in view of the teachings of Yan et al. Yan et al. teach the addition of dexamethasone to their culture media (Yan, paragraphs, 178 and 330) that grows bone marrow cells (Yan, paragraph 85) in a microgravity environment (Yan, paragraph 111) for bone marrow transplantation (Yan, paragraph 43) which is the same purpose as Goodwin et al. It would have been obvious to someone skilled in the art to add dexamethasone to the culture medium since Yan et al. and Goodwin #1 share the same purpose, see M.P.E.P. § 2144.06.

Furthermore both the addition of TGF- β and dexamethasone to the culture medium would be seen as obvious improvements to the known technique of Goodwin #1 since both improve the production of cartilage tissue in traditional culture methods (KSR International Co. v. Teleflex Inc., 550 U.S.--, 82 USPQ2d 1385 (2007)) .

Therefore, the invention as a whole would have been prima facie obvious at the time of filing in view of the references listed above and as such claims 1-5, 7 and 9 are not allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until

after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

In response to this office action the applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thane Underdahl whose telephone number is (571) 272-9042. The examiner can normally be reached Monday through Thursday, 8:00 to 17:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Thane Underdahl
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/Leon B Lankford/
Primary Examiner, Art Unit 1651